With the Author's Kind regards

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ON THE ACTION

OF

APOMORPHINE AND APOCODEINE,

WITH REFERENCE TO THEIR VALUE AS EXPECTORANTS IN THE TREATMENT OF CHRONIC BRONCHITIS.

ROYAL COLLEGE OF SURGEONS OF ENGLAND
25 MAR 91

BY

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ON THE ACTION OF APOMORPHINE AND APOCODEINE, WITH REFERENCE TO THEIR VALUE AS EXPECTORANTS IN THE TREATMENT OF CHRONIC BRONCHITIS.

A.—Apomorphine.

The discovery of apomorphine is usually ascribed to Matthiessen and Wright, although there is reason to suppose that they were to some extent forestalled by Arppe. At a meeting of the Royal Society held on June 10th, 1869, Mr. Augustus Matthiessen and Mr. C. R. A. Wright read a paper received on May 6th of the same year, "On the Action of Hydrochloric Acid on Morphine,"[1] and in this communication they gave particulars of the mode of preparing a substance, for which they proposed the name of "apomorphia." It is not necessary to give all the details of their method, but it practically amounted to this, that they took some morphine, sealed it up in a tube with a large excess of hydrochloric acid, and kept it at a temperature of from 140° to 150° for two or three hours. On breaking open the tube it was found to contain the hydrochlorate of the new base apomorphine. It was purified by dissolving in water, adding an excess of bicarbonate of sodium, and extracting the precipitate with ether or chloroform. On shaking up the solution with hydrochloric acid the sides of the vessel became coated with crystals of the hydrochlorate. These were drained from the mother liquor, washed with cold water, recrystallised from hot water, and dried on bibulous paper, or over sulphuric acid. This was the way in which they originally obtained their apomorphine, but they found on further investigation that the new base might also be prepared by digesting morphine with excess of hydrochloric acid for some days on a water bath under paraffin. In this process the morphine loses a molecule of water, and becomes converted into apomorphine (morphine, $C_{17}H_{19}NO_3 = H_2O + C_{17}H_{17}NO_2$, apomorphine). They found that apomorphine might also be obtained by heating codeine with hydrochloric acid according to the formula (codeine, $C_{17}H_{17}(CH_3)HNO_3 + HCl = CH_3Cl + H_2O + C_{17}H_{17}NO_2$, apomorphine). It is probable that in this reaction there is an intermediate product, but with this we are not for the moment concerned.

These same observers showed that apomorphine was formed when morphine was heated with dilute sulphuric acid in sealed tubes for some hours at a temperature of from 140° to 150°. This is pretty much what was done nearly a quarter of a century previously by Arppe,[2] his product, which was probably an impure sulphate of apomorphine, being subsequently named by Laurent and Gerhardt "sulphomorphide." This sulphomorphide turned green on exposure to light and air, and gave the reactions now ascribed to apomorphine.

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[1] *Proceedings of th Royal Society*, vol. xvii, p. 455.

[2] "Uber eine merkwürdige Veränderung des Morphins durch Schwefelsäure, *Annalen der Chemie und Pharmacie*, vol. xl, 1845, p. 96.

In a paper by Matthiessen and Burnside,[3] the authors called attention to the fact that apomorphine might be prepared by heating morphine with chloride of zinc. This method of manufacture seems to have been suggested by E. L. Mayer,[4] who worked at the subject in conjunction with Matthiessen. The hydrochlorate of apomorphine prepared by these different methods was distinctly crystalline, and its crystalline form was determined by Professor W. H. Miller.[5] When exposed for some time to the action of air and light it turned green, probably from oxidation. The reason for supposing that the change in colour was due to oxidisation was that, under these conditions, the salt increased in weight. The green mass was soluble in water, communicating to the solution a bright emerald green colour. It dissolved in alcohol, forming a green solution in ether and benzol, giving a magnificent rose purple, and in chloroform a violet pink. It was found, too, that it gave certain characteristic colour reactions with nitric acid, perchloride of iron, and other reagents.

Some of the specimens of apomorphine obtained by Matthiessen and Wright were submitted for investigation to Dr. Gee, who published two papers on the subject. The first of these was read before the Clinical Society,[6] and the second was published in the *St. Bartholomew's Hospital Reports*.[7] Dr. Gee established the fact that when the hydrochlorate of apomorphine was injected subcutaneously in doses of a tenth of a grain, it acted as a speedy emetic. He also mentioned the circumstance that "a gentleman who was working with the new base, and who had his hands sometimes wetted with the solutions, frequently vomited three or four times in the course of the evening," presumably from its absorption by the skin. Dr. Gee seems also to have supposed that it acted equally well as an emetic when taken by the mouth, for he quoted the case of a man who, after taking ⅛ of a grain, "felt dizzy and depressed, with an uncomfortable sensation in the head, and vomited freely in twenty-five minutes." That this was not regarded as exceptional seems to be established by the fact that in a summary of the advantages of the drug, Dr. Gee says: "As much can be raised by the tip of the little finger as will cause vomiting when taken by the mouth," and in his second paper he adds: "To the best of my knowledge apomorphine has never been administered in an emetic dose (namely, 1/10 grain subcutaneously, or ¼ grain by the mouth) without producing speedy vomiting."

During the next four or five years a good many papers appeared on the action and properties of apomorphine, the most noteworthy contributions being by Dujardin-Beaumetz, of Paris;[8] Siebert, of Dorpat;[9] Max Quehl—[10] under the direction of Professor Köhler—Bourgeois;[11] Routy;[12] Carville;

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[3] *Proceedings of the Royal Society*, vol. xix, 1871, p. 71.

[4] *Berichte deutsch. chem. Gesell.* Berlin, 1871, vol. iv, p. 121.

[5] *Proceedings of the Royal Society*, vol. xviii, p. 88.

[6] On the Action of a New Organic Base, Apomorphia, *Transactions of the Clinical Society*, vol. ii, 1869, p. 166.

[7] Note upon Apomorphia and Chloroeodide, vol. v, 1869, p. 215.

[8] *Bulletin Général de Thérapeutique*, October 30th, 1874.

[9] *Untersuchungen ueber die physiologischen Wirkungen des Apomorphins*, Dorpat, 1871.

[10] *Ueber die physiologischen Wirkungen des Apomorphins*, Halle, 1872.

[11] *De l'Apomorphine, Recherches cliniques sur un nouvel Emétique*, Paris, 1874.

[12] *De l'Emploi de l'Apomorphine comme Vomitif administrée par Injection hypodermique*, Paris, 1874.

Charcot; Chouppe;[13] Trousseau and Pidoux; Théodore Verger;[14] Vulpian and Juratsz.[15] Reichert, in an inaugural thesis published in 1880, gave an elaborate account of its physiological action, but no serious attempt seems to have been made to controvert the statement that it uniformly acted as an emetic when administered in small doses by the stomach. It was pretty generally accepted that it produced emesis by whatever channel it was introduced into the system, and that solutions could not be employed with safety when once they had commenced to change colour.

In 1881, being anxious to obtain a good emetic for use in cases of poisoning, I made some observations on apomorphine, and found: (1) That it acted promptly as an emetic when injected hypodermically. (2) That no emetic effect was produced when given by the stomach in small doses. (3) That its properties were not impaired by keeping; and (4) That it differed so completely in action from morphine that there was no reason why it should not be given as an emetic in cases of poisoning by opium. As a proof that the drug does not deteriorate by keeping, I may mention that I gave a patient a hypodermic injection of 4½ minims of a 1 in 50 solution of the hydrochlorate, which had been exposed to the light for three months, and had assumed a dark green colour, and in less than two minutes it acted powerfully, and completely evacuated the stomach. Six months later I used the same solution in the same dose for another patient, and it acted equally promptly, the patient vomiting at intervals for over an hour.

In the *British Pharmacopœia* of 1885, the injectio apomorphinæ hypodermica (1 in 50) was made official, with the misleading direction that "the solution should be made as required for use." About this time attention was directed on the Continent to the use of apomorphine as an expectorant. Juratsz recommended it for internal use for this purpose in doses of from $\frac{1}{65}$ to $\frac{1}{22}$ of a grain. He gave it in a mixture with simple syrup and a few drops of hydrochloric acid. In 1881 Beck[16] advocated its use in doses of $\frac{1}{8}$ of a grain every three or four hours; and in 1882 Rossbach[17] published some cases in which he had administered it in doses of from 5 milligrammes to 1 centigramme, or from $\frac{1}{13}$ to $\frac{1}{6}$ of a grain. Dr. Wertner,[18] of Wartberg, in Hungary, used it in doses of 2 centigrammes, or $\frac{1}{3}$ of a grain. One of Wertner's cases is interesting, the patient having by accident taken, without serious inconvenience, ten times the dose intended, or over 3 grains. The only English writer who appears to have paid any attention to the subject is Dr. Charteris, of Glasgow, who in a communication published in 1881 mentions casually that on two occasions he gave $\frac{1}{12}$ of a grain by mouth without any bad result.

Some three years ago, whilst casting about for a new expectorant for use in cases of bronchitis, I determined to try the hydrochlorate of apomorphine by mouth. My first endeavour was to determine the dose. At first I gave it in very small doses, for I was impressed by Dr. Gee's very positive statement that in doses of $\frac{1}{4}$ of a grain it uniformly acted as an emetic. I had to feel my way cautiously, for the majority of my patients were out-patients whom I saw but once a week, and I was especially anxious to avoid giving anything like an overdose. For convenience of dispensing, I usually employed a 1 per cent. solution, and not the 2 per cent. solution of the *Pharmacopœia*. I began with a 5-minim dose (gr. $\frac{1}{20}$), and worked my way up drop by drop until I found that the majority of my patients could take a grain of apomorphine three times a day without inconvenience. Of late I have considerably exceeded this dose, and I have now under treatment several patients who take 1½ or 2 grains three times a day without any difficulty. I have not kept notes of all the cases treated by this method, but I have full notes of forty patients who have been under observation during the present winter. The majority were out-patients at the Westminster Hospital, a few were under my care in the wards, and a still smaller number were private patients. With one or two exceptions, to which I will presently refer, they were all suffering with what for the sake of convenience may be called "winter cough," that is to say, bronchial catarrh or chronic bronchitis with or without emphysema. Some of the patients were men, others were women. The list included a man aged 76, another aged 71, a third aged 70, and two children whose ages were respectively 5 months and 7 months.

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[13] *Gaz. hebd.*, December, 1874.

[14] *Bull. de Thérap.*, No. 32, p. 499, 1877.

[15] *Centralblatt f. d. med. Wiss.*, p. 499, 1874.

[16] *Deutsche med. Wochen.*, February, 1881.

[17] *Berlin. klin. Wochen.*, No. 27.

[18] *Pest. med.-chir. Presse*, No. 18 and 19, 1882

On finding that such large doses could be given with impunity, I experienced some doubt as to the purity of the drug. I made inquiries as to the source of the supply, and found that several different specimens had been used for making the solution, and that they had been obtained in the ordinary course from the chemists who supply the hospital with drugs. Most of them were crystalline, and answered to the ordinary description of apomorphine as given in the *Pharmacopœia*, but one or two were amorphous. I tested them, and found that they all gave the ordinary colour reactions with nitric acid and with perchloride of iron, as described by Matthiessen and Wright, and adopted in the *British Pharmacopœia*.

It was obviously necessary to ascertain if the apomorphine I was using would produce an emetic effect if injected hypodermically. In out-patient practice it is rarely necessary to give emetics, but fortunately there happened to be in the wards a lad of 16 for whom an emetic was required. He was admitted for chorea, but was suddenly seized with an acute attack of dyspepsia. The house-physician, Mr. A. M. Cato, gave him, at my suggestion, a hypodermic injection of 5 minims of a 2 per cent. solution of the hydrochlorate dispensed from the particular specimen of the drug at that time in use for the out-patients; it had not been long prepared, but was dark green in colour. The injection was administered in the forearm, and the patient vomited in thirty-five seconds. The onset of the vomiting was so sudden that he had no time to avail himself of the porringer which had been placed in readiness, but deposited the contents of his stomach on the floor. The vomiting continued at intervals for four or five hours, with much relief to the patient. His chorea seemed to be so much better that on the 25th he was ordered 5 minims of the same solution three times a day by mouth On December 2nd this was increased to 10 minims, on the 8th to 15 minims, on the 9th to 30 minims, and on the 16th to 40 minims without the production of any emetic effect. The medicine was given in the ordinary course, and there was no doubt that he took it. One thing was perfectly clear, that a patient who was made violent sick by ⅙ of a grain given hypodermically could take ⅞ of a grain by mouth three times a day, or 2⅝ grains daily, without the slightest inconvenience.

In the majority of cases the apomorphine was given in the form of solution, but in one or two cases I had it made into pills. A patient, aged 21, came to me suffering from well-marked phthisis. He had had a cough for three years, and had on four occasions suffered from profuse hæmoptysis. He had a moist cavity at the base of the right lung, and rhonchus was to be heard all over the chest on both sides. On December 21st I ordered him ⅒ of a grain of hydrochlorate of apomorphine, to be taken three times a day, and on the 28th ¼ of a grain three times a day. On the 31st the dose was increased to ½ a grain three times a day, and on January 4th to 1 grain three times a day. The pills were taken after meals, and the only effect was to make him expectorate very freely. On January 6th he was ordered a pill containing 1¼ grain three times a day. He took twelve pills, and then complained that they made him feel rather sick, but not enough to cause him any inconvenience. On January 10th he was ordered 1½ grain three times a day, and this seems to have exhausted his capabilities in this direction, for he took only five of them and said he was unable to continue the treatment on account of the nausea they produced. I may mention that this was not a hospital patient, and that every precaution was taken to obtain a reliable specimen of the drug.

Although these large doses of apomorphine, when given by mouth, failed to produce either nausea or emesis, they exerted a powerful expectorant action in cases of chronic bronchitis. I give a brief abstract of a typical case which occurred in hospital practice.

W. A., aged 67, is a horsekeeper by occupation, and is engaged in omnibus work. Is in the yard exposed to all weathers from 6 in the morning till 8 at night. Is well enough in the summer, but has had a bad cough every winter for the last fifteen years. He coughs all day, and expectorates in the intervals. Has lost flesh a little this winter, but not more than usual. On examination it is found that the chest is emphysematous, that expiration is prolonged, and that there is moist rhonchus all over, but especially at the bases posteriorly. On November 12th he was ordered ½ a drachm of the 1 per cent. solution three times a day, with syrup of tar. On November 15th he reported that he had expectorated a great deal, and to use his own words, he "regular vomited it up;" but he was not sick. The dose was increased to 1 drachm three times a day. On the 19th he said that the phlegm came up "much easier," and that the medicine "cleared the chest," and "made the breath freer." The dose was increased to 1½ drachm, and on the 22nd, the improvement still continuing, to 2 drachms three times a day. On December 3rd he was ordered 3 drachms three times a day. He reported that after the first dose he brought up in about half an hour quite half a pint of thick yellow phlegm; it was all phlegm each time, and there was no food with it. On December 6th the dose was increased to 200 minims three times a day, or 6 grains daily. This, too, gave him great relief and caused him no inconvenience. There was no headache and no nausea. This apomorphine, when given to another patient hypodermically in a dose of $\frac{1}{20}$ of a grain, produced vomiting in less than a minute. I have no doubt that for the production of its expectorant action large doses are much more efficacious than small ones.

In a few cases apomorphine given by mouth produced nausea and vomiting. One patient, an Irish-American, and a gas worker by occupation, had taken a drachm of the 1 per cent. solution three times a day for ten days without complaint. He was then ordered two drachms of the same solution once a day. Three days later he returned, and said that it had made him violently sick. On inquiry, it was found that he had taken it in the morning on an empty stomach. He was directed to take it after breakfast, and from that time experienced no inconvenience. The dose was subsequently increased to two and a half drachms three times a day, but there was no further complaint.

An almost identical case was that of a woman, aged 52. She was ordered a drachm of the 1 per cent. solution once a day for four days, and took it every morning before breakfast. Three mornings it made her feel sick, and on the fourth she actually vomited. She was then told to take the medicine immediately after dinner, and did so for four days without vomiting or experiencing any nausea. She was then ordered 1½ drachm once a day. Two mornings she took it before breakfast and was sick, and on the other two days she took it after breakfast and was not sick. She then took 2½ drachms three times a day without difficulty, and subsequently 3 drachms three times a day, or 5.4 grains a day, with much benefit to the chronic bronchitis from which she suffered.

Even when the patient complains of nausea it does not follow that it is due to the action of the drug. A hysterical girl of 17 complained that she was sick after each dose, but as on investigation it was found that she was sick "as soon as she looked at the bottle," very little importance was attached to her statement. A patient, age 33, a carman, was admitted into the wards suffering from phthisis, the physical signs being dulness at both apices and deficient movement, with coarse breathing all over the left front. He was ordered ½ a drachm of the 1 per cent. solution three times a day, and suffered from an attack of vomiting every morning. The medicine was at once discontinued, but the vomiting persisted, and was evidently the result of the violent cough from which he suffered, especially in the morning. A small dose of morphine promptly arrested it.

It is somewhat difficult to reconcile my results with those obtained by Dr. Gee. It may be urged that the specimens used by him, having been obtained direct from Matthiessen and Wright, were pure, whilst mine were adulterated. The fact that my specimens gave the ordinary reactions of apomorphine cannot be accepted as conclusive evidence that they were pure, for it must be remembered that the colour tests for apomorphine are very delicate, and that a small percentage of the drug mixed with some inert substance, such as sugar of milk, would give them almost equally well. One point in favour of the purity of the specimens I employed was that most of them were crystalline. My colleague, Dr. Dupré, very kindly undertook an examination of the specimen, which had been chiefly employed in making the solution, and was of opinion that it was pure. It not only gave the chemical reactions of apomorphine, but, on microscopical examination, it was seen that almost every particle was distinctly crystalline. He was satisfied that the impurity, if any, did not amount to more than 1 per cent.

It may, too, be urged that my solutions had undergone some chemical change by long keeping, and that they had deteriorated. In answer to this, I may say that although some of the solutions employed had been prepared for some time and had turned green, others were made as required for use and dispensed on the spot. An argument against the age of the specimen being the important factor is to be found in the fact already quoted, that a 2 per cent. solution which had been kept exposed to the light for a period of six months acted promptly as an emetic when injected hypodermically.

Then, too, it might be said that as I usually commenced with small doses and worked up to big ones a condition of tolerance was in some cases established. This explanation will not suffice, for in some cases I commenced with half-drachm or drachm doses of the 1 per cent. solution three times a day. Possibly the substance which we now call apomorphine is not identical with that submitted to Dr. Gee twenty years ago. There are, as we know, some four or five different methods of preparing apomorphine, and it may be that the product is not identical in every case. This is a possible explanation, but not at all a likely one. At all events, I know experimentally that the action of apomorphine prepared from codeine is identical with that of the apomorphine prepared from morphine.

Another possible explanation is that apomorphine, being a somewhat unstable body, undergoes some chemical change in the stomach. This, again, is not probable, for it will be remembered that hydrochloric acid is used in the preparation of the alkaloid, and there is no reason for supposing that the pepsin would in any way alter its chemical composition. The rate of absorption has probably more to do with it. When injected hypodermically it is absorbed at once, but when mixed with food in the stomach it is probably absorbed comparatively slowly. The fact that apomorphine administered on an empty stomach produces vomiting more readily than when given after meals throws some light on the subject.

With the view of testing the question of the rapidity of absorption I administered what would be an emetic dose of apomorphine if given hypodermically in the form of an ointment. I had three specimens prepared, one with lard, one with vaseline, and one with lanoline, each containing ⅒ of a grain to the drachm. They were given to three different patients, with instructions that they should be rubbed into the chest before the fire at bedtime. They produced no emetic effect. The strength of the ointment was then increased in each case to ½ of a grain, and the result was the same. I subsequently employed an ointment containing a grain of apomorphine mixed with an ounce of lard or lanoline, directing the patient to rub in half the quantity on two consecutive nights. It acted as an expectorant, the effect lasting for some hours, but it induced no nausea. I repeated this in several cases, and the result was always the same. I presume that the fact of the drug being comparatively slowly absorbed affords an explanation of what at first sight appears an anomalous result. Practically it is a decided advantage to have at our disposal a drug which may be relied on to induce an expectorant effect when used in the form of an ointment. In the case of children suffering from bronchitis it is simply invaluable.

I have also employed apomorphine as a spray, on the lines of the old ipecacuanha wine treatment. I used for its administration a bottle with a conical bottom, the silver tube reaching to the apex, so that the whole of the solution could be utilised. I took care to observe the recognised precautions in such cases, using a warm solution, making the patient spit out the fluid which accumulated in the mouth, instructing him not to arch his tongue against the roof of the mouth, and making him inspire deeply with every contraction of the air ball. I began with 10 minims of the 1 per cent. solution in a little water for each inhalation, but I now frequently give as much as half a drachm at a dose. The expectorant effect is very marked, especially with the large doses. The results have exceeded my expectations, and I hope to give details of this method of treatment in a future communication. The point of interest with regard to the action of apomorphine is, that a dose which would act as an emetic, if administered hypodermically, can be used as an inhalation without inducing this effect.

Several writers have stated that apomorphine may, under exceptional circumstances, induce narcotic effects. I have notes of three cases which bear on this point; the first was a patient, aged 67, a stockbroker, who was under treatment for chronic bronchitis. I prescribed a mixture containing 10 minims of the 2 per cent. solution of hydrochlorate of apomorphine to be taken three times a day. He returned at the expiration of a week, and said that the medicine had made him expectorate freely, but that he could not continue taking it, as it made him so sleepy. On expressing my surprise, he added that "morphine always disagreed with him." He had evidently been trying to read my prescription, and detecting, as he thought, the word "morphia," had experienced the sensations which from former experience he had been accustomed to associate with that drug. On explaining the matter to him, he was perfectly satisfied, and continued taking the drug without any further complaint as to its narcotic action. I may mention incidentally that several of my patients have objected to taking "apomorphine" on the ground that "morphine never agreed with them." In another case, a patient, aged 58, a cattle salesman, took a drachm of the 1 per cent. solution three times a day for a week without difficulty. I then increased the dose to 2 drachms three times a day, and the patient complained that it gave him a sharp pain across the forehead and over the bridge of the nose, and made him feel so sleepy, that he could hardly keep his eyes open. Curiously enough, on increasing the dose to 2¼ drachms three times a day, he made no complaint. The medicine was then discontinued, but a month later he was given a drachm and a half three times a day. It caused him no inconvenience until the fifth day, when there was a slight return of the drowsiness and headache. He again discontinued taking it. Mr. Betts, the house-surgeon at the Westminster Hospital, gave a casualty patient 5 minims of the same solution hypodermically, and it not only failed to produce vomiting, but made him drowsy, and contracted his pupils. This result was so exceptional that I am inclined to think that the apomorphine must in some inexplicable manner have become mixed with morphine. The specimen was submitted to Dr. Dupré for examination, but unfortunately the quantity was too small to enable him to give a decided opinion. It will be remembered that ether is used as a solvent in the preparation of apomorphine, and it is usually stated that morphine is insoluble in that menstruum, but I am informed on reliable authority that this insolubility is not complete. Professor Wormley, in his *Micro-chemistry of Poisons*,[19] states that morphine requires 7,725 parts of absolute ether for its solution, and that commercial ether dissolves one part of the alkaloid in 4,225 parts of the liquid.

There is no reason why apomorphine should not be given in combination with morphine. Rossbach speaks highly of this mixture in the treatment of phthisis, and says that it lessens the frequency of the cough and increases the fluidity of the sputum. Lauder Brunton says: "When apomorphine and morphine are given together, they do not destroy each other's action, so that from the combination we get increased secretion from the mucous membrane, with diminished irritability of the respiratory centre, and consequently lessened cough. The cases in which the combination is useful are those where there is difficulty in breathing, continual cough, and thick tenacious mucus."

In the majority of cases of winter cough which have been under treatment I have given the apomorphine in a mixture flavoured with either syrup of Virginian prune, syrup of tar, or syrup of lemons. I do not know that this is the best form in which to give it, especially as in some cases the mixture after a time assumes a dirty green colour; but there are so many colour reactions for apomorphine that our pharmacists should have no difficulty in devising a formula which would meet this objection.

I have treated a few cases of bronchorrhœa with small doses of apomorphine with success. On November 5th, Dr. Edgeworth, of Bristol, wrote to me saying that he had suffered from a cough every year for many winters, and that fifty or sixty times a day he expectorated a large quantity of frothy phlegm. I ventured to suggest that he should take $\frac{1}{12}$ of a grain of apomorphine in a teaspoonful of syrup of tar every two or three hours. On December 9th he wrote saying that the expectoration had been reduced by quite one-half, and that he rarely expectorated more than twelve times a day. He added that at first he had experienced some difficulty in taking the syrup of tar made according to the *United States Pharmacopœia* formula, but that on substituting glycerine for the sugar the difficulty had at once disappeared. He says: "I think the alteration is a good one for general use," and in this expression of opinion I certainly agree with him. In the French *Codex* there is a preparation of tar known as "glycéré de goudron," but it is made with glycerine of starch and not with glycerine.

Apomorphine has in addition been used with success for a variety of purposes: to remove foreign bodies from the œsophagus, to ward off an attack of epilepsy, to check hæmoptysis and *post-partum* hæmorrhage, and in the treatment of chorea, laryngismus stridulus, and whooping-cough.

B.—APOCODEINE.

In 1869 Matthiessen and Wright published two papers[20] on the Action of Hydrochloric Acid on Codeia, but seem to have experienced some difficulty in arriving at any definite result. In 1870 Matthiessen and Burnside published a paper[21] on the Action of Chloride of Zinc on Codeia, in which they describe in minute detail the method of obtaining apocodeine when hydrochlorate of codeia is heated for fifteen minutes at a temperature of from 170° to 180° C. with a concentrated solution of chloride of zinc, decomposition taking place according to the reaction: (codeine, $C_{18}H_{21}NO_3 = H_2O + C_{18}H_{19}NO_2$, apocodeine). On cooling, a yellowish-brown tarry mass separates from the liquid, and may on further cooling be drawn into thin threads, and obtained almost free from the excess of chloride of zinc. This amorphous silk-like mass is almost pure hydrochlorate of apocodeine. To obtain the base the hydrochlorate is dissolved in hot water and precipitated by hydrochloric acid. The liquid containing the precipitated hydrochlorate is allowed to cool, and the precipitate on solidifying is separated from the acid solution. The operation of dissolving and reprecipitating with hydrochloric acid is repeated several times, and lastly the hydrochlorate is dissolved in water, precipitated with carbonate of sodium, and the base extracted with ether. On evaporating the solution in ether, the base remains behind as an amorphous gum-like reddish mass, which is subsequently powdered and dried in a water bath.

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[19] J. B. Lippincott, Philadelphia, 1885.

[20] *Proceedings of the Royal Society*, vol. xvii, p. 460, and vol. xviii, p. 83.

Apocodeine itself is soluble in alcohol, ether, and chloroform, but is almost insoluble in water, and has not been obtained in a crystalline form. The hydrochlorate obtained by shaking the solution of the pure base in ether with hydrochloric acid and evaporating to dryness is freely soluble in water, but is not crystalline. The action of reagents on apomorphine and on apocodeine is almost identical, with the exception that the blood-red colour yielded with nitric acid is much more permanent with apocodeine than with apomorphine. Between the two bases a marked difference was found to exist with respect to stability, apocodeine being in this respect far in advance of apomorphine; the hydrochlorates also differ, for the apomorphine salt is crystalline whilst the apocodeine is amorphous. The preparation of apocodeine is easy and simple, yielding a very large product, and in this respect, too, it differs very materially from apomorphine, the preparation of which is tedious whilst the yield is uncertain.

The apocodeine prepared by Matthiessen and Burnside was submitted for examination to Dr. J. Wickham Legg, who, in a paper entitled "Observations on the Physiological Action of Apocodeia and of the Hydrochlorate of Cotarnamic Acid,"[22] reported that "when given in doses of 1, 2, or 3 grains to a healthy man no appreciable effect was produced." He added: "It is obvious that apocodeine is wholly unfitted for subcutaneous injection. In the only instance in which it was practised $\frac{1}{10}$ of a grain injected under the skin of the forearm produced great redness, tingling, and considerable suffering for more than a week." His observations appear not to have been carried beyond this point.

Dr. Dujardin-Beaumetz states that apocodeine possesses all the therapeutic properties of apomorphine, but in a modified degree. He says that it is an emetic, and has been found useful in the treatment of hæmoptysis, croup, and whooping-cough. He recommends it hypodermically in doses of ¼ grain and by the mouth in doses of ⅔ grain. I have been unable to find any other account of the use of the drug in the treatment of disease.

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[21] *Ibid.*, vol. xix, p. 71.

[22] *St. Bartholomew's Hospital Reports*, vol. vi, p 97

In 1881, whilst working at apomorphine, I made some observations with apocodeine with the view of ascertaining its possible value as an emetic in cases of poisoning. I took care to obtain a reliable specimen, and administered to two patients hypodermically 15 minims of a freshly prepared 1 in 50 solution, but without exciting either nausea or vomiting. Both patients vomited promptly after an injection of 5 minims of a 1 in 50 solution of hydrochlorate of apomorphine. The hydrochlorate of apocodeine employed was amorphous.

During the last few months I have repeated these observations. A patient, aged 48, was under my care suffering from chronic bronchitis. His cough was very violent, he was emphysematous, and moist rhonchus was to be heard in abundance over both front and back. On November 5th I gave him an injection of 5 minims of a 1 per cent. solution of hydrochlorate of apocodeine, but no effect was produced. On November 8th I gave him an injection of 15 minims of the same solution. In eleven minutes he commenced expectorating freely, and the expectoration continued during the rest of the day. He was not sick, and there was no irritation at the seat of injection. On November 12th he was given an injection of 15 minims of the solution in the right arm, and 5 minims in the left. He again expectorated freely, but there was neither nausea nor vomiting. This time he complained that the injection made his arm sore. There was a good deal of tenderness and swelling, which persisted for some days, but there was no abscess. I tested the solution with litmus paper, and found that it was acid. I then reverted to the specimen of apocodeine used in 1881, and had a 1 in 50 solution prepared which was perfectly neutral. The same patient was given an injection of 20 minims of this solution—10 in the right arm and 10 in the left. This, too, acted as a powerful expectorant, but fortunately produced very little local irritation.

A freshly prepared specimen of the salt having been placed at my disposal, it was made into a 1 in 50 solution, and used in the case of a man aged 31, a gas stoker, who for many years had suffered from chronic bronchitis. On January 6th a hypodermic injection was given of 10 minims in each arm, or ⅖ of a grain. He reported that he felt "a little bit queer" after the injection "just for a moment," but it did not make him, feel sick. The arms smarted just a little for about an hour, but he did not notice anything the matter with them after that. On January 9th the same solution was used, and he was given a hypodermic injection of 10 minims in the right arm, and 15 in the left, or ½ of a grain in all. It caused him to expectorate very freely, but he suffered no inconvenience and the smarting in the arms was very slight. The solution employed in the case was perfectly neutral. In the face of these observations I cannot confirm Dr. Wickham Legg's statement that apocodeine is "wholly unfitted for subcutaneous injection." All that is necessary is to use a neutral solution.

In six cases I have used apocodeine by mouth as an expectorant with satisfactory results. The first patient was 70 years of age, and had long been under treatment. On September

24th he was ordered 10 minims of a 1 per cent. solution three times a day; on October 1st the dose was increased to 20 minims three times a day; on October 9th to 25 minims; and on October 29th to half a drachm. He expectorated very freely indeed, especially after the larger doses, but there was no complaint of nausea or vomiting. In the case of another patient, aged 71, the dose was gradually increased from 10 minims to half a drachm three times a day, and again it answered well as an expectorant, and produced no disagreeable symptoms. This patient in six weeks took 28 grains of apocodeine. In one case, and one only, the apocodeine produced nausea and vomiting. The patient was a boy, aged 17, an artist's model, who suffered from neurotic asthma. From April 23rd to June 25th he was on apomorphine, the dose being gradually increased from 15 to 50 minims three times a day. During this period he took nearly a drachm of the hydrochlorate of apomorphine, not only without the production of any unpleasant symptom, but with marked relief to his attacks of dyspnœa. On July 16th he was ordered 5 minims of the 1 per cent. solution of apocodeine three times a day, the dose being week by week increased by 5 minims at a dose. There was no complaint until, on October 1st, the patient was ordered 20 minims three times a day. He then stated that it made him feel sick, and that he was "unable to keep it down." He took twelve doses, and usually vomited about two hours after each dose. On October 8th the dose was reduced to 15 minims three times a day, which he took without difficulty. On October 15th the dose was again increased to 20 minims three times a day, and this he took for a fortnight without suffering from vomiting, although he admitted that he usually felt sick after each dose. He took in all 24 grains of apocodeine.

The hydrochlorate of apocodeine acts as a powerful expectorant when given in the form of pill. From 3 to 4 grains may be administered daily with perfect safety.

These observations on apocodeine are admittedly incomplete, but the supply of material at my command was limited.